

Addressing the Interface of Anemia, Hemorrhage and Adverse Pregnancy Outcomes

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Preventable Deaths Every Day

- 830 women die during pregnancy and childbirth everyday
- 287,000 maternal deaths every year (total 303,000)
- 56,000 maternal deaths every year in India

WHO, State of World's Mothers Report 2015



Why Do Women Die?

- Major complications account for 80% of all maternal deaths
- Severe bleeding (primary PPH) – 35%
- ↑ - BP (eclampsia, pre-eclampsia) – > 15 %
- Infections (usually manifest post delivery)
- Confounders include underlying anemia, malaria, HIV/AIDS and TB

WHO, 2012

Anemia in Pregnancy

- Anemia in pregnancy is the major contributor or sole cause of 20-40% of maternal deaths
 - (estimated to affect 41.8% of all pregnant women world)
- Accounts for 8.8% of total disability from all conditions

de Benoist B et al., eds. Worldwide prevalence of anemia 1993-2005, WHO, 2008

Bailey, RL et al., the Epidemiology of Global Micronutrient Deficiencies, 2015

Kassebaum, et al., A Systematic Analysis of Global Anemia Burden from 1990 to 2010, 2018

The Lower the Hemoglobin the Worse the Pregnancy Outcomes for Mother and Baby

- In mothers –
 - ↑ in postpartum hemorrhage
 - ↑ in C/S
 - ↑ in sepsis
 - ↑ preterm births (the leading cause of < 5 mortality)
- In newborns –
 - ↑ low birthweight
 - ↑ stillbirths
 - ↓ cognitive performance
 - ↓ physical growth
 - ↑ behavioral deficits

Lozoff B, Iron deficiency and child development, 2007

Iron Demands in Pregnancy

Are increased 2-3X's to:

- Address an increase in fluid volume (30%)
- Support the growing fetus (especially in the 2nd half of pregnancy)
- Account for blood loss at delivery

Ferritin Level

- Measurement of hemoglobin alone is insufficient to determine who will benefit from supplemental iron
- Ferritin is a protein that stores iron and releases it in a controlled fashion
- We now know that maternal levels of serum ferritin of <15 mcg/L predict inadequate iron to the fetal brain
- Once this occurs, the impact to the infant and child is irreversible

Lozoff B et al., Long-Lasting Neural and Behavioral Effects of Iron Deficiency in Infancy, 2018.

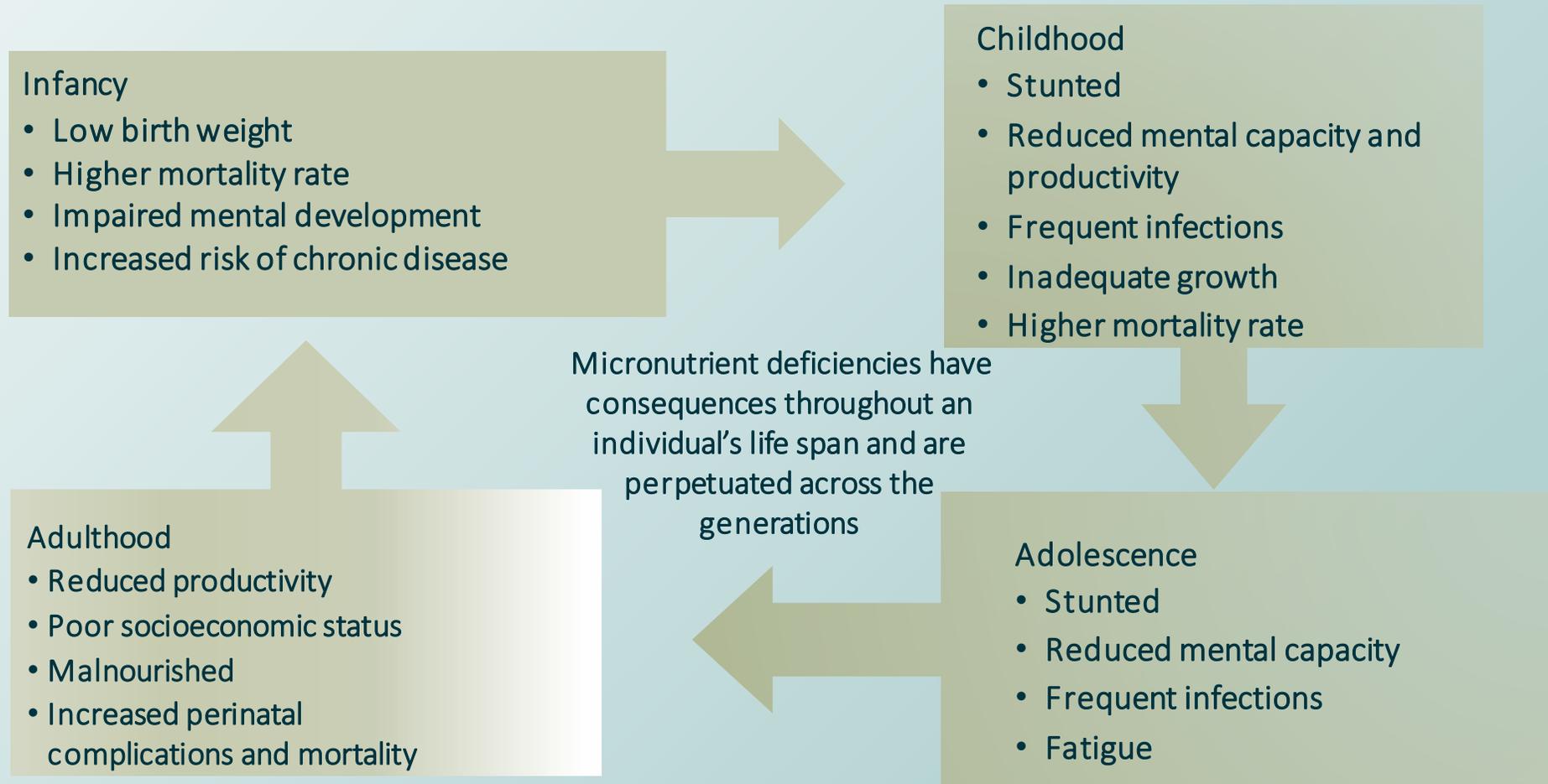
Hallberg L et al., Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women, 1993

Iron Intake

- Despite all national programs supporting supplementation with oral iron, little has changed over the past 40 years
 - Side effects
 - Adherence
 - Poor absorption

Auerbach M, Macdougall I, Oral Iron Therapy: After Three Centuries, It Is Time for a Change, 2016

Intergenerational Impact



Adapted from Bailey. R, et al, The Epidemiology of Global Micronutrient Deficiencies, 2015(NIH) Annals of Nutrition and Metabolism

British Blood Transfusion Society Recommendation

- Intravenous iron should be considered in women with severe IDA (hemoglobin < 8 gm/dL) or in any newly diagnosed anemia beyond 34 weeks of gestation
- Hemoglobin with < 10 mg/dL may not allow the transfer of sufficient iron to the newborn
- Should be considered in women with confirmed IDA who fail to respond or are intolerant to oral iron

www.bbts.org.uk (amended)

New Approach

- One new therapeutic approach is the expanded use of IV Iron
 - New formulations (4) allow for reduction of anemia (up to 95%) with a single infusion
 - No major serious adverse events in multiple randomized prospective trials from the developed world (> 100 published studies, including its use in pregnancy)
 - Acute need for research to study maternal and infant outcomes in countries where rates of moderate/severe anemia are highest

Auerbach M, Macdougall I. Oral Iron Therapy: After Three Centuries, It Is Time for a Change, 2016

The RAPIDIRON Trial

Two primary outcomes:

- Rate of conversion to a non-anemic state (≥ 11 g/dL) at the time of delivery.
(Consistent with GoI strategy to reduce anemia by 3%/year)
- Rate of low birthweight (under 2500 gms)
(VLBW rates will also be reported)

This reflects a composite outcome, as PTB and IUGR are often associated with low birth weight

The Challenge

- Every 4 minutes a woman dies from postpartum hemorrhage (PPH – 35% of all maternal deaths)
- Global action to address PPH comprehensively is a public health imperative.

USAID/CHIP 2012/ACOG, 2015

Average Interval from Onset to Death

- Ruptured uterus 24 hours
- Antepartum hemorrhage 12 hours
- Postpartum hemorrhage 2 hours (dire implications for women with moderate/severe anemia)

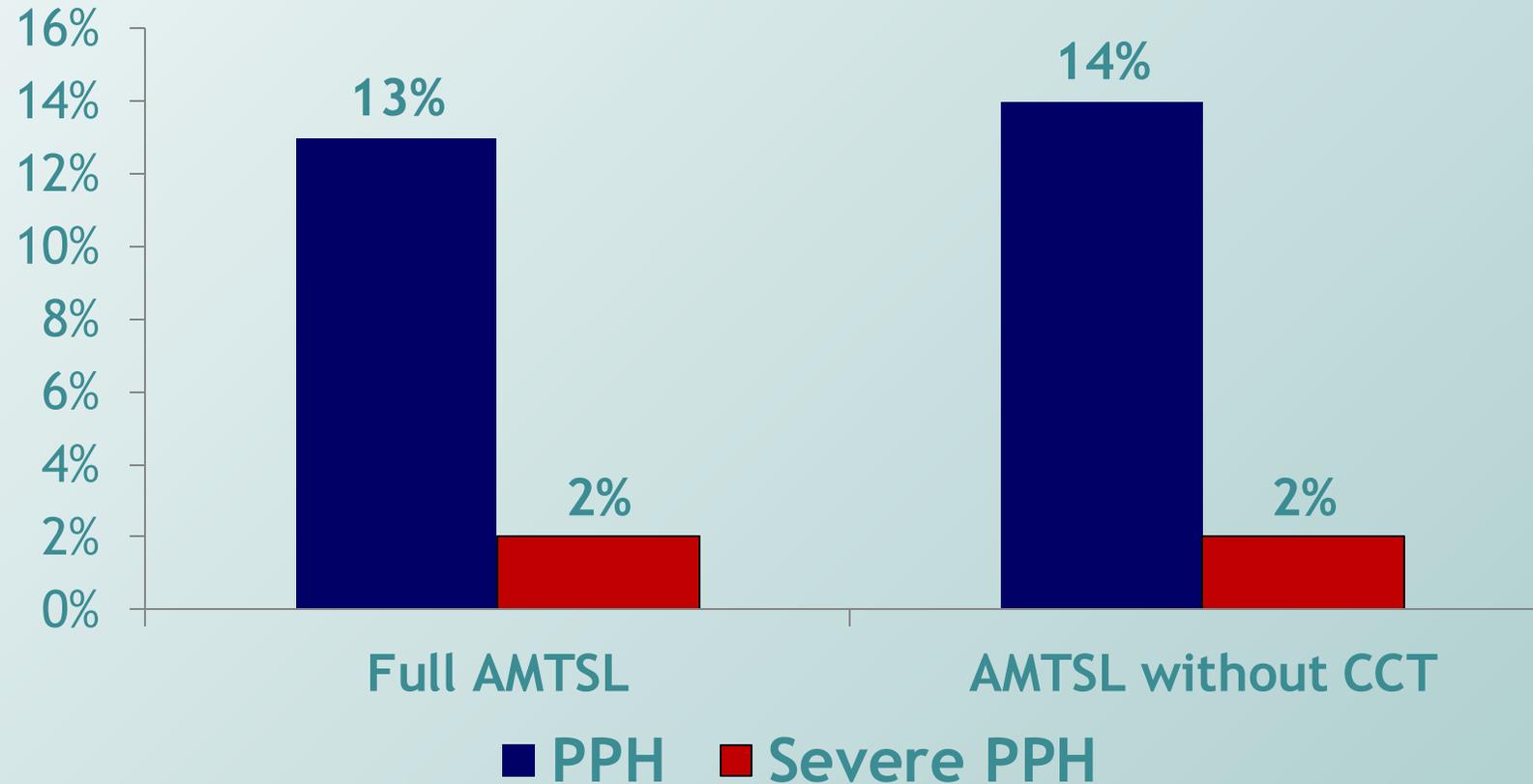
Maine D. Safe Motherhood Programs: Options and Issues,
Center for Population & Family Health, Columbia University, 1993

What have we learned about reducing the incidence of PPH from hundreds of published clinical trials?

Active Management of 3rd Stage of Labor

- 5 randomized trials
- Cochrane review
- N = > 6,000
- NNT: Prevent PPH 500 ml - 12
- Severe PPH 1000 ml - 55

AMTSL with and without CCT on PPH prevention



Gülmezoglu et al, Active management of the third stage of labour with and without controlled cord traction: a randomised, controlled, non-inferiority trial. Lancet. 2012

Uterotonic Drugs

- Oxytocin-posterior pituitary extract
- Ergometrine-preparation of ergot
- Syntometrine-combination of oxytocin and ergometrine
- Misoprostol-prostaglandin E1 analogue
- Carbetocin (large multi-site clinical trial)

Global Network for Women's and Children's Health Research

Primary Hypothesis

Misoprostol administered during the third stage of labor will significantly reduce the incidence of acute postpartum hemorrhage by 50%.

N=1600

Measuring postpartum blood loss

- BRASSS-V[®] blood collection drape with calibrated receptacle
- The drape is used in both arms



Patel A, *et al.* Drape estimation vs. visual assessment for estimating postpartum hemorrhage. *Int J Gynaecol Obstet.* 2006 Jun

Number Needed to Treat (NNT)

One case of postpartum hemorrhage was prevented for every 18 women who received misoprostol

PPH ↓ 47%

Severe PPH ↓ 80%

India: Misoprostol to Prevent PPH

THE LANCET



Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial

Richard J Derman, Bhalchandra S Kodkany, Shivaprasad S Goudar, Stacie E Geller, Vijaya A Naik, M B Bellad, Shobhana S Patted, Ashlesha Patel, Stanley A Edlavitch, Tyler Hartwell, Hrishikesh Chakraborty, Nancy Moss

Lancet 2006; 368: 1248-53

Misoprostol for Self-Administration

- Uganda (Mama Miso Study)
- Indonesia (JHPEIGO)
- Afghanistan (JHPEIGO)
- Liberia (JHPEIGO)
- Papua New Guinea
- Tanzania
- Ethiopia
- Nigeria
- Lao People's Democratic Republic

Misoprostol Registration Completed



Management of PPH Low Resource Settings

Uterine tamponade

- 90% of PPH in under-resourced countries due to uterine atony
- Hydrostatic Balloon Catheters

Sayeba Akhter, Use of a Condom to Control Massive Postpartum Hemorrhage,
www.medscape.com/viewarticle/459894

Tying the condom to the catheter



Non-inflatable Anti-shock Garment



New Drugs to Prevent or Treat PPH

Tranexamic Acid

- Prevents breakdown of fibrin and helps to maintain clotting
- Cochrane review-
 - 12 trials (N=3285) ↓ blood loss after delivery
- WOMAN trial
 - N=20,000 – 20% reduction in blood loss

Carbetocin - heat stable relative of oxytocin

- Positive side effect profile
- Significant reduction in post-c/s blood loss
- Major WHO trial (includes our site) ongoing

Maternal Mortality Due to PPH in the Developing World

- Lack of antepartum screening and treatment for anemia
- Poor access to skilled providers/suppliers
- Poor transport systems
- Poor emergency services
- Poor clinic/hospital infrastructure
- ↑ in unnecessary C/S
- Need for team training, including the use of simulation

The best predictor of a pregnancy outcome....
is the state of health of a women...
when she first enters pregnancy

Special Thanks

